

REMARKS/ARGUMENTS

Status

Claims 155-159 and 161-179 are pending. Claims 168 and 172-178 are withdrawn and claims 155-159, 161-167, 169-171 and 179 are under examination. In the most recent Office Action, claims 155, 156, 158, 159, 161-167 and 169-171 were allowed, and claims 157 and 179 were rejected under Section 112, first paragraph (new matter). Claim 179 has been amended without disclaimer or prejudice to future prosecution. The rejections and amendment are discussed below. In addition, Applicants discuss EMBL Accession Number AC006517 (cited in the accompanying information disclosure statement).

Claim 157

The Office states that the recitation in claim 157 of "human" referring to human monoclonal antibodies is not supported in the specification. Applicants respectfully disagree. Human monoclonal antibodies are described, *inter alia*, at paragraphs [0148] and [0149] of the specification. The Office incorrectly states paragraph 149 describes "human polyclonal antibodies produced in mice." The technique described in paragraph [0149] includes the use of "classical hybridoma technology" which, as the skilled reader would immediately recognize, results in production of *monoclonal* antibodies. The attention of the Office is also respectfully directed to paragraph [0148] which states "Methods of generating new DC-specific antigen-binding fragments . . . includes . . . immunizing mammals with the antigen and generating polyclonal or mAbs [monoclonal antibodies]." Paragraphs [0148] and [0149] describe human monoclonal antibodies.

Applicants note that human monoclonal antibodies are also *enabled* by the specification. Methods for producing human monoclonal antibodies to a specific antigen were known at the priority date of the instant application, including the use of transgenic mammals as described in paragraph [0149]. For the examiner's reference, a copy of the Mendez et al. article referred to in paragraph [0149] is enclosed, along with a review article published in 2002 describing the use of transgenic mice for production of human monoclonal antibodies [Kellermann and Green, 2002 "Antibody discovery: the use of transgenic mice to generate human monoclonal antibodies for

therapeutics." *Curr Opin Biotechnol.* 13:593-7]. This technology is also well described in the patent literature (a small selection of patents focused on this technology include Pat. Nos. 6,300,129; 6,255,458; 5,789,650; and 5,625,126). Further, although paragraph [0149] describes production of human monoclonal antibodies using transgenic mice, other methods of preparing monoclonal human antibodies, not involving transgenic mammals, were well known at the date the present application was filed. For example, production of human monoclonal antibodies by *in vitro* immunization of human B cells was well known. See, for example, Koda et al., 1990, "Generation of human monoclonal antibodies against colon cancer" *Arch Surg.* 125:1591-7; Borrebaeck et al., 1988, "Human monoclonal antibodies produced by primary *in vitro* immunization of peripheral blood lymphocytes" *Proc. Nat'l Acad. Sci* 85:3995-99; Dueñas et al., 1996, "In vitro immunization of naive human B cells yields high affinity immunoglobulin G antibodies as illustrated by phage display" *Immunology* 89:1.¹ It is not necessary, nor desirable, to teach in the specification what is already known in the art. One of ordinary skill in the art, informed by the instant specification of the properties of BDCA-2, was able to produce human monoclonal antibodies using routine methods.

Thus, Applicants respectfully submit that Claim 157 is fully supported by the specification, and request that this rejection be withdrawn.

Claim 179

The Office states that Claim 179 is not supported because the Office believes that the element "a label that can be conjugated to an antigen-binding fragment" is not described in the specification. Applicants respectfully disagree. However, in the interest of expediting prosecution, Claim 179 has been amended to delete this phrase. The term "label" added by this amendment finds support at paragraph [0208]. The phrase "a reagent capable of combining with the antigen binding fragment after the antigen binding fragment binds an antigen" added by this amendment also finds support at paragraph [0208]. (Although paragraph [0208] literally recites "a **second** reagent capable of combining with the **first reagent** after **it has found its target**" it is clear that the first reagent can be an antigen binding fragment, and "its target" is an antigen. It is

¹ For the convenience of the Examiner, copies are enclosed

not required that the claim use the literal words of the specification; the specification need only convey to the reader that the inventors possessed the invention described in the claims.)

Applicants submit that Claim 157, as amended, is in condition for allowance.

EMBL Accession Number AC006517

Applicants have cited EMBL Accession Number AC006517 (hereinafter "AC006517") in an IDS concurrently filed. This accession number was cited by a foreign patent office (EPO) and Applicants wish to make the citation of record.² The same accession number is referred to at paragraph [0308] of the instant specification as a GenBank sequence.

AC006517 presents a nucleotide sequence which is stated to be a "WORKING DRAFT SEQUENCE, 63 unordered pieces." It appears that the AC006517 discloses at least a part of the sequence of human chromosome 12. It is furthermore noted that AC006517 states that the sequence described consists of 63 contigs whose true order was not known and whose order in AC006517 reference is arbitrary. An acknowledgement is also made in AC006517 that the sequence disclosed is unfinished.

The sequence in AC006517 is an unordered 218,414 nucleotides in length, while the BDCA-2 cDNA is only 1312 nucleotides in length. Attached herewith is an alignment between the cDNA sequence for BDCA-2 and the genomic sequence from chromosome 12 (i.e. as comprised in the sequence of AC006517). It is noted that there is not 100% identity between the two sequences.

Also attached is a document which shows where the exons of BDCA-2 lie. As can be seen, the exons 5-7 are inverted and run in the incorrect orientation to the first four exons. This means that, even if the skilled person had been provided with the fragmented, inverted, genomic sequence illustrated in AC006517, it would not have been possible to identify the BDCA-2 encoding sequence as a protein coding sequence. In order to do this the skilled person would have needed knowledge of the BDCA-2 cDNA sequence.

Accordingly, Applicants submit that AC006517 did not describe or suggest the BDCA-2 antigen-binding fragments of the present invention.

² Release 61, issued 22-Oct-1999 was cited by the EPO and is submitted and discussed here.

Request for Rejoinder

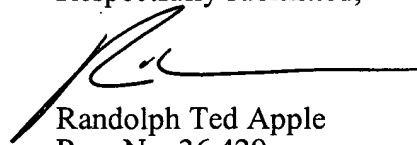
Applicants note that claims 168 and 172-178 each depend, directly or indirectly, from allowed claims. Applicants submit that the patentability of the claimed antigen-binding fragment comprising a polypeptide domain that specifically binds a BDCA-2 protein has been established and that the patentability of the dependent claims incorporating the antigen-binding fragment can be examined with little burden on the Office. Applicants respectfully submit that there is especially little burden in examining claims 168 and 172-176. In contrast it would be a substantial burden, measured in both expense and time, for Applicants to file additional applications. Accordingly, Applicants respectfully urge the Office to rejoin the claims.

CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance and an action to that end is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 650-326-2400.

Respectfully submitted,



Randolph Ted Apple
Reg. No. 36,429

Enclosures

1. Exhibit 1 (alignment between the cDNA sequence for BDCA-2 and AC006517 sequence from chromosome 12)
2. Exhibit 2 (table showing position of BDCA-2 exons in AC006517)

TOWNSEND and TOWNSEND and CREW LLP
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San Francisco, California 94111-3834
Tel: 650-326-2400
Fax: 415-576-0300
Attachments
RTA:sj
60270813 v1

AC006517.17|AC006517 Homo sapiens chromosome 12 clone RP11-277J24, WORKING
DRAFT SEQUENCE,
21 unordered pieces
Length = 172062

Score = 718 bits (362), Expect = 0.0
Identities = 362/362 (100%)
Strand = Plus / Plus

Query: 1 cagtgattctcgtgcctcagcctcctgagtagccgaaattacagacgtgtgccaccatgc 60
|||||
Sbjct: 73781 cagtgattctcgtgcctcagcctcctgagtagccgaaattacagacgtgtgccaccatgc 73840

Query: 61 ttggctaattttttggatttttagtagagatggggtttccactatgttggccaggctagtc 120
|||||
Sbjct: 73841 ttggctaattttttggatttttagtagagatggggtttccactatgttggccaggctagtc 73900

Query: 121 ttgaactcctggcctgaagcaatccgcccacctcagcctcccaaagtgtgagattatag 180
|||||
Sbjct: 73901 ttgaactcctggcctgaagcaatccgcccacctcagcctcccaaagtgtgagattatag 73960

Query: 181 gcacgagccactacacctggccacaaaattctttaagaagccaatcccatcctccctca 240
|||||
Sbjct: 73961 gcacgagccactacacctggccacaaaattctttaagaagccaatcccatcctccctca 74020

Query: 241 agagccaagggggccacctcaccctcttggttacagcagatcctgcctcccacagtcaccct 300
|||||
Sbjct: 74021 agagccaagggggccacctcaccctcttggttacagcagatcctgcctcccacagtcaccct 74080

Query: 301 gctcccaagtgcacacctctgtctgacctgcatgggtgtgcggtgccctcctgcctcaggc 360
|||||
Sbjct: 74081 gctcccaagtgcacacctctgtctgacctgcatgggtgtgcggtgccctcctgcctcaggc 74140

Query: 361 cg 362
||
Sbjct: 74141 cg 74142

Score = 585 bits (295), Expect = e-164
Identities = 295/295 (100%)
Strand = Plus / Minus

Query: 989 attctggcactcaggtgaacccaataaccttgatgagcgttgtgcgataataaatttccg 1048
|||||
Sbjct: 55775 attctggcactcaggtgaacccaataaccttgatgagcgttgtgcgataataaatttccg 55716

Query: 1049 ttcttcagaagaatggggctggaatgacattcactgtcatgtacctcagaagtcaatttg 1108
|||||
Sbjct: 55715 ttcttcagaagaatggggctggaatgacattcactgtcatgtacctcagaagtcaatttg 55656

Query: 1109 caagatgaagaagatctacatatataatgaaatattctccctggaaatgtgtttgggttg 1168
|||||
Sbjct: 55655 caagatgaagaagatctacatatataatgaaatattctccctggaaatgtgtttgggttg 55596

Query: 1169 catccaccgtttagaaagctaaattgattttttaatttatgtgtaagttttgtacaagg 1228
|||||
Sbjct: 55595 catccaccgtttagaaagctaaattgattttttaatttatgtgtaagttttgtacaagg 55536

Query: 1229 aatgccctaaaaatgtttcagcaggctgtcacctattacacttatgatataatcc 1283
|||||
Sbjct: 55535 aatgccctaaaaatgtttcagcaggctgtcacctattacacttatgatataatcc 55481

Score = 319 bits (161), Expect = 3e-84
Identities = 161/161 (100%)
Strand = Plus / Plus

Query: 362 gcgaagaaggatctaagggttggcttgtttgaaagaaccacaccccgaaagtaacatct 421
|||||
Sbjct: 75776 gcgaagaaggatctaagggttggcttgtttgaaagaaccacaccccgaaagtaacatct 75835

Query: 422 ttggagaaagtatacaagagcttctgcacccacctgatagaggaagtccaaagggtgtg 481
|||||
Sbjct: 75836 ttggagaaagtatacaagagcttctgcacccacctgatagaggaagtccaaagggtgtg 75895

Query: 482 cgcacacacaatggtgcctgaagaagagcctcaagaccgag 522
|||||
Sbjct: 75896 cgcacacacaatggtgcctgaagaagagcctcaagaccgag 75936

Score = 299 bits (151), Expect = 3e-78
Identities = 151/151 (100%)
Strand = Plus / Minus

Query: 723 gaagattggagctgctgcccaccccttggaacttcatttcagtctagttgctactttatt 782
|||||
Sbjct: 145448 gaagattggagctgctgcccaccccttggaacttcatttcagtctagttgctactttatt 145389

Query: 783 tctactgggatgcaatcttgactaagagtcaaaagaactgttctgtgatgggggctgat 842
|||||
Sbjct: 145388 tctactgggatgcaatcttgactaagagtcaaaagaactgttctgtgatgggggctgat 145329

Query: 843 ctggtggtgatcaacaccaggaagaacagg 873
|||||
Sbjct: 145328 ctggtggtgatcaacaccaggaagaacagg 145298

Score = 236 bits (119), Expect = 3e-59
Identities = 119/119 (100%)
Strand = Plus / Minus

Query: 870 caggatttcattcattcagaatctgaaaagaaattcttcttattttctggggctgtcagat 929
|||||
Sbjct: 56950 caggatttcattcattcagaatctgaaaagaaattcttcttattttctggggctgtcagat 56891

Query: 930 ccagggggtcggcgacattggcaatgggttgaccagacaccatacaatgaaaatgtcac 988

|||||
Sbjct: 56890 ccagggggtcggcgacattggcaatgggttgaccagacaccataacaatgaaaatgtcac 56832

Score = 222 bits (112), Expect = 5e-55
Identities = 112/112 (100%)
Strand = Plus / Plus

Query: 615 gtgcctcacaattttatgtatagcaaaactgtcaagaggctgtccaagttacgagagtat 674
|||||
Sbjct: 81723 gtgcctcacaattttatgtatagcaaaactgtcaagaggctgtccaagttacgagagtat 81782

Query: 675 caacagtatcatccaagcctgacctgcgctcatggaaggaaaggacatagaag 726
|||||
Sbjct: 81783 caacagtatcatccaagcctgacctgcgctcatggaaggaaaggacatagaag 81834

Score = 188 bits (95), Expect = 7e-45
Identities = 95/95 (100%)
Strand = Plus / Plus

Query: 521 agagaaaggactctggtggttccagttgaaggtctggtccatggcagtcgtatccatctt 580
|||||
Sbjct: 76829 agagaaaggactctggtggttccagttgaaggtctggtccatggcagtcgtatccatctt 76888

Query: 581 gctcctcagtgtctgtttcactgtgagttctgtgg 615
|||||
Sbjct: 76889 gctcctcagtgtctgtttcactgtgagttctgtgg 76923

Score = 159 bits (80), Expect = 6e-36
Identities = 162/188 (86%), Gaps = 1/188 (0%)
Strand = Plus / Minus

Query: 5 gattctcgtgcctcagcctcctgagtagccgaaattacagacgtgtgccaccatgcttgg 64
|||||
Sbjct: 49211 gattctcgtgcctcagcctcctgagtagctgggattacaggcgtccgcccaccatgcccgg 49152

Query: 65 ctaattttttggatttttagtagagatggggtttcactatgttggccaggctagtcttga 124
|||||
Sbjct: 49151 ctaatttttt-gtatttttagtagagatgaggtttcacaacattggccaggctggtcttga 49093

Query: 125 actcctggcctgaagcaatccgcccacctcagcctcccaaagtgtgagattataggcac 184
|||||
Sbjct: 49092 actcctgacctcaggtaatccaccgcctcagcctcccaaagtgtggaattacaggcat 49033

Query: 185 gagccact 192
|||||
Sbjct: 49032 gagccact 49025

Score = 135 bits (68), Expect = 9e-29
Identities = 170/203 (83%), Gaps = 2/203 (0%)
Strand = Plus / Plus

Query: 2 agtgattctcgtgcctcagcctcctgagtagccgaaattacagacgtgtgccaccatgct 61
||||||| ||| ||||||||||||| | ||||| | | |||||||
Sbjct: 54482 agtgattctcctgcttcagcctcctgagtagctgggattacaggcatccaccaccatgcc 54541

Query: 62 tggctaattttttggatttttagtagagatggggtttcactatggttgccaggctagtct 121
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Sbjct: 54542 tggctaatttttgagtttttagtagagacggcgtttcacatggttgccaggctggtct 54601

Query: 122 tgaactcctggcctgaagcaatccgcccacctcagcctcccaaagtgtgagattatagg 181
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Sbjct: 54602 tgaactcctgacct--cgtgatccaccacctcgccctcccaaagtgtgggattacagg 54659

Query: 182 cacgagccactacacctggccac 204
| ||||| ||| |||||
Sbjct: 54660 cgtgagccaccgcacccggccac 54682

Score = 135 bits (68), Expect = 9e-29
Identities = 159/188 (84%), Gaps = 1/188 (0%)
Strand = Plus / Plus

Query: 5 gattctcgtgcctcagcctcctgagtagccgaaattacagacgtgtgccaccatgcttgg 64
|||||| ||||||||||| ||||| | | || || || |||||||||||
Sbjct: 119808 gattctcgtgcctcagcctcccaaagttagctgggactataggcgccctgccaccatgcttgg 119867

Query: 65 ctaatt-ttttggatttttagtagagatggggtttcactatggttgccaggctagtcttg 123
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Sbjct: 119868 ctaattttttgaatttttagtagagattgggttcacatggttgccaggctggttttg 119927

Query: 124 aactcctggcctgaagcaatccgcccacctcagcctcccaaagtgtgagattataggca 183
||||||| | ||| |||| || ||||||||||| ||||| |||||
Sbjct: 119928 aactcctgacttcaagtgatccaccggcctcagcctcccaaagtgttaggattacaggca 119987

Query: 184 cgagccac 191
|||||||
Sbjct: 119988 tgagccac 119995

Score = 131 bits (66), Expect = 1e-27
Identities = 124/142 (87%), Gaps = 1/142 (0%)
Strand = Plus / Plus

Query: 51 gccaccatgcttggctaattttttggatttttagtagagatggggtttcactatggtggc 110
|||||| ||| ||||||||| |||| ||||||||||| ||||||||| || |||||
Sbjct: 107363 gccaccacgctcggctaatt-tttgtatttttagtagagatggggtttcacatattggc 107421

Query: 111 caggctagtcttgaactcctggcctgaagcaatccgcccacctcagcctcccaaagtgt 170
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Sbjct: 107422 catgctagtctcgaactcctgaccttacgtgatccgcccacctcagcctcctaaagtgt 107481

Query: 171 gagattataggcacgagccact 192
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Sbjct: 107482 aagcttacaggcatgagccact 107503

Score = 131 bits (66), Expect = 1e-27
Identities = 124/142 (87%), Gaps = 1/142 (0%)
Strand = Plus / Minus

Query: 51 gccaccatgcttggttaatttttggatttttagtagagatggggtttcactatgttggc 110
||||||| ||| ||||||||| ||| ||||||||| ||||||||| ||| |||||
Sbjct: 169901 gccaccacgctcggctaattt-ttgtatttttagtagagatggggtttcaccatattggc 169843

Query: 111 caggctagtcttgaactcctggcctgaagcaatccgcccacctcagcctcccaaagtgt 170
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Sbjct: 169842 catgctagtctcgaactcctgaccttacgtgatccgcccacctcagcctcctaaagtgt 169783

Query: 171 gagattataggcacgagccact 192
|| ||| ||||| |||||||
Sbjct: 169782 aagcttacaggcatgagccact 169761

Score = 125 bits (63), Expect = 9e-26
Identities = 163/194 (84%), Gaps = 3/194 (1%)
Strand = Plus / Minus

Query: 5 gattctcgtgcctcagcctcctgagtagcgaattacagacgtgtgccaccatgcttgg 64
||||||| ||||||||| ||||||||| ||| ||||| ||| ||||| |||||
Sbjct: 29870 gattctcctgcctcagcctcctgagtagctggaattacaaacacatgccaccatccttgg 29811

Query: 65 ctaattttttggatttttagtagagatggggtttcactatgttggccaggctagtcttga 124
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Sbjct: 29810 ctaattt-ttgtatttttagtagagacaggattttaccatgttggtcaggctggtctoga 29752

Query: 125 actcctggcctgaagcaatccgcccacctcagcctcccaaagtgtgagattataggcac 184
||||||| ||| ||| ||||||| ||||| ||||||||| ||||| ||||| |||||
Sbjct: 29751 actcctgacct--cgtgatccgcccgcctcgccctcccaaagtgtgggattacaggcgt 29694

Query: 185 gagccactacacct 198
||||||| |||||
Sbjct: 29693 gagccactgcacct 29680

Score = 121 bits (61), Expect = 1e-24
Identities = 106/121 (87%)
Strand = Plus / Minus

Query: 77 atttttagtagagatggggtttcactatgttggccaggctagtcttgaactcctggcctg 136
||||||||| ||||| ||| ||||||||| ||| ||||| ||||| ||||| |||||
Sbjct: 119369 atttttagtagagatggtgttttaccatgttggccaagctggtctccaactcctgacctc 119310

Query: 137 aagcaatccgcccacctcagcctcccaaagtgtgagattataggcacgagccactacac 196
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Sbjct: 119309 aggtgatccgcccacctcagcctcccaaagtgtgagattacaggcatgagccaccacac 119250

Query: 197 c 197
Sbjct: 119249 c 119249

Score = 115 bits (58), Expect = 8e-23
Identities = 159/190 (83%), Gaps = 2/190 (1%)
Strand = Plus / Plus

Query: 2 agtgattctcgtgcctcagcctcctgagtagccgaaattacagacgtgtgccaccatgct 61
||||||| ||||||| ||||| | | ||||| | |||||||
Sbjct: 142519 agtgattctcgtgcctcagcctcccgagtaactgtgattacaggcatgtgccaccatgcc 142578

Query: 62 tggctaatttttggatttttagtagagatggggtttcactatgttgccaggctagtct 121
||||||| | ||||||| || |||| | ||||||| ||||
Sbjct: 142579 gagctaattttt-gtatttttagtagagaagg-gtttcgccatgttgccaggctggtct 142636

Query: 122 tgaactcctggcctgaagcaatccgcccacctcagcctcccaaagtgtgagattatagg 181
||||||| ||||| | ||| || ||||||| ||||| |
Sbjct: 142637 caaactcctgacctgaggtgatccaccgcctcagcctcccaaagtgtgaggattacaag 142696

Query: 182 cacgagccac 191
|| |||||
Sbjct: 142697 catgagccac 142706

Score = 111 bits (56), Expect = 1e-21
Identities = 158/191 (82%), Gaps = 2/191 (1%)
Strand = Plus / Minus

Query: 2 agtgattctcgtgcctcagcctcctgagtagccgaaattacagacgtgtgccaccatgct 61
||||||| ||||||| ||||||| ||||| || || ||||| |
Sbjct: 11929 agtgattctcgtgcctcagcctcctgagtagctggaattataggcatgcaccaccacacc 11870

Query: 62 tggctaatttttggatttttagtagagatggggtttcactatgttgccaggctagtct 121
||||||| ||||||| ||||||| ||||||| ||||| |||||
Sbjct: 11869 tggctaatttttgtatttttagtagagacggggtttcacatgttagccaggatggtct 11810

Query: 122 tgaactcctggcctgaagcaatccgcccacctcagcctcccaaagtgtgagattatagg 181
| ||||| ||| | ||| |||| |||| ||||||| ||||| |||
Sbjct: 11809 caatctcctgacct--cgtgatctgccgcctcggcctcccaaagtgtgggattacagg 11752

Query: 182 cacgagccact 192
| |||||
Sbjct: 11751 cgtgagccact 11741

Score = 111 bits (56), Expect = 1e-21
Identities = 145/171 (84%), Gaps = 4/171 (2%)
Strand = Plus / Plus

Query: 2 agtgattctcgtgcctcagcctcctgagtagccgaaattac-agacgtgtgccaccatgc 60
||||||| ||||||| ||||||| ||||| ||||| ||||| ||
Sbjct: 80528 agtgattctcgtgcctcagcctcctgagtagctgggattaatagacacgtgtcaccacgc 80587

Query: 61 ttggctaatttttttgatttttagtagagatgggggtttcactatgttggccaggctagtc 120
||||||| |||| |
Sbjct: 80588 ctggctaatt-tttgtatttttagtagagatgggggtttcaccatgtcgggcaggctggtc 80646

Query: 121 ttgaactcctggcctgaagcaatccgcccacctcagcctcccaaagtgtg 171
| ||||| ||| | | |||| |
Sbjct: 80647 tcaaactcctgacctcatg--atccacccacctcggcctcccaaagtgtg 80695

Score = 111 bits (56), Expect = 1e-21
Identities = 144/172 (83%), Gaps = 1/172 (0%)
Strand = Plus / Plus

Query: 6 attctcgtgcctcagcctcctgagtagccgaaattacagaagtggtgccaccatgcttggc 65
||||| ||||| ||||| | ||||| | ||||| ||| ||
Sbjct: 47373 attctcctgcctcagcctcccagtagctgggattacagggtgcctgccacctgcctagc 47432

Query: 66 taatttttttgatttttagtagagatgggggtttcactatgttggccaggctagtccttgaa 125
||||| |||| |
Sbjct: 47433 taatt-tttgtatttttagtagagacgggggtttcaccacattggccaggcgatctggaa 47491

Query: 126 ctctggcctgaagcaatccgcccacctcagcctcccaaagtgtgagatta 177
||||| ||| | |||| |
Sbjct: 47492 ctctgacctcaggcaatgcgcccacctcagcctcccaaagtgtgggatta 47543

**Position of BDCA-2 exons within the human genomic sequence of
chromosome 12
(EMBL accession number : AC006517)**

mRNA position	Genomic DNA position	Orientation
1-361	73781-74141	+
362-522	76831-76923	+
523-615	75776-75936	+
616-726	81724-81834	+
727-872	145444-145299	-
873-988	56947-56832	-
989-1283	55775-55481	-